REMARKS

The present invention relates to methods for modulating the expression of a gene in a subject that contains one or more cells comprising: a gene of interest under the control of a steroid or steroid-like hormone response element; an ultraspiracle receptor; and a receptor that, in the presence of its cognate ligand and the ultraspiracle receptor, binds to the steroid or steroid-like hormone response element. By contacting such cells with the cognate ligand, the expression of the gene of interest can be modulated.

Claims 14-19 and 35-53 are currently pending in the instant application, with claims 49-53 having been withdrawn from consideration due to a provisional election in response to a restriction requirement. Applicants have amended claim 17 herein. The claim amendments are not made for reasons of patentability, but instead to assist the Examiner in understanding the claimed invention. For example, the amendments to claim 17 replace the phrases "wild type gene" and "therapeutic gene" with their definitions provided in the specification, *e.g.*, on page 17, lines 1-34.

Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer claimed in the instant application in one or more applications which may claim priority hereto. Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Restriction Requirement

The Examiner has divided the claims as follows:

Group I: Claims 14-19 and 35-48;

Group II: Claim 49;

Group III: Claims 50-52; and

Group IV: Claim 53.

Applicants affirm the provisional election of Group I (claims 14-19 and 35-48). The non-elected claims are retained in the instant application, pending final disposition of the application.

Non Art-Related Remarks

35 U.S.C § 112, First Paragraph

The rejection of claims 14-19 and 35-48 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. Applicants respectfully disagree with the Examiner's assertion that the specification does not enable the skilled artisan to use the invention commensurate with the scope of the claims.

The standard for determining enablement is whether the specification as filed provides sufficient information as to permit one skilled in the art to make and use the claimed invention. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988). The test of enablement is not whether experimentation is necessary, but rather whether any experimentation that is necessary is undue. *Id.* A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

As discussed above, the instantly claimed invention relates to methods for modulating the expression of a gene in a subject that contains one or more cells comprising: a gene of interest under the control of a steroid or steroid-like hormone response element; an ultraspiracle receptor; and a receptor that, in the presence of a cognate ligand and the ultraspiracle receptor, binds to the steroid or steroid-like hormone response element. The methods of the claimed invention comprise administering to the subject an amount of ligand effective to modulate the expression of the gene of interest.

Applicants respectfully disagree with the Examiner's assertion that the instant specification "does not provide guidance or example that would [enable] by correlation the instant methods as the[y] are drawn to nucleic acid-based therapies." Paper No. 5, paragraph

bridging pages 4 and 5. Indeed, this assertion is contrary to the admission by the Examiner that the instant specification provides an enabling disclosure for such methods using cells in culture, which, as discussed below, reasonably correlates to the scope of the instant claims.

First, it is respectfully submitted that the Examiner has taken an unduly narrow position as to the requirements of the instantly claimed methods. Specifically, the Examiner erroneously asserts that the claims "are drawn to nucleic acid therapy and involve methods of introducing and expressing exogenous genes and nucleic acid sequences in specific cells in a whole animal." Paper No. 5, page 4. This assertion reflects an erroneous determination that the claims require delivery of DNA constructs into cells while the cells are in the subject. Applicants note that there is no such requirement in the instant claims. Furthermore, the skilled artisan will understand that *ex vivo* strategies can be used to provide DNA constructs useful for carrying out the instantly claimed methods; *i.e.*, methods in which DNA constructs can be inserted into cells, *e.g.*, in culture, and the resulting cells introduced into subjects for various purposes, including therapeutic purposes. *See, e.g.*, specification, page 19, lines 29-35, and page 21, lines 23-28; *see also*, R.G. Crystal, *Science* 270: 404-410 (1995), Table 2 (describing successful *ex vivo* gene therapy strategies).

Moreover, the Examiner concedes that the methods described in the instant specification for modulating gene expression in cultured cells meet the enablement standards of 35 U.S.C. § 112. Based on the knowledge of *ex vivo* strategies in the art, the skilled artisan would understand that methods for manipulating gene expression in cultured cells could also be used for manipulating gene expression in subjects. Therefore, because the instant specification "discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim," the enablement requirement of 35 U.S.C. § 112 is satisfied. *See*, MPEP § 2164.01(b).

Second, Applicants also disagree with the Examiner's assertion that (referring to Verma and Somia, *Nature* 389: 239-242 (1997)) because obstacles remain in the practice of gene therapy, the instant claims do not meet the enablement standard. Paper No. 5, page 6. It is

respectfully submitted that this assertion reflects an unduly narrow position regarding the ability of the artisan to introduce nucleic acids into cells in subjects generally.

The standard for determining enablement requires only that the skilled artisan be able to make and use the invention without undue experimentation. In the instant case, methods for introducing DNA constructs into subjects, both *in vivo* and *ex vivo*, are well known to the skilled artisan. *See, e.g.*, R.G. Crystal, page 405, right column ("Although gene transfer has not been demonstrated in all recipients, most studies have shown that genes can be transferred... whether the strategy is *ex vivo* or *in vivo*..., with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies."). Thus, the belief that "obstacles" may remain before gene therapy can be used routinely for human therapeutic purposes is irrelevant to the instant methods. The fact is that the skilled artisan can readily introduce DNA constructs into subjects, using only well known methods and with only a level of experimentation typically engaged in by the artisan. *See*, MPEP § 2164.01 (the fact that experimentation may be complex does not make it undue if the art typically engages in such experimentation).

Moreover, the instant invention is not directed to gene therapy *per se*, but to any of a number of possible applications based on the realization that gene expression can be modulated using a receptor that, in the presence of the ultraspiracle receptor and a ligand, binds to steroid hormone response elements. Furthermore, the instant specification provides extensive guidance for methods for modulating genes in cultured cells. Based on the level of skill in the art, one of ordinary skill could practice the instantly claimed invention using only the teachings of the specification and the knowledge readily available to the skilled artisan, whether an *ex vivo* or *in vivo* strategy is employed. *See*, MPEP § 2164.01 (a patent need not teach, and preferably omits, that which is well known in the art).

Accordingly, because the claims meet the enablement standard of 35 U.S.C. § 112, first paragraph, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

35 U.S.C § 112, Second Paragraph

The rejection of claim 17, under 35 U.S.C § 112, second paragraph, as allegedly being indefinite for reciting the phrases "exogenous genes, "wild type genes," and "therapeutic genes," is respectfully traversed.

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed. Cir. 1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed. Cir. 1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.") (emphasis added).

In the instant case, each of the phrases is defined in the instant specification in sufficient detail to reasonably apprise the skilled artisan of its meaning. *See, e.g.*, specification, page 16, line 27, through page 18, line 28.

Nevertheless, in an effort to advance prosecution, Applicants have replaced these terms in the claims with an appropriate definition taken from the specification. Applicants respectfully submit that the foregoing claim amendments render this rejection moot.

CONCLUSION

In view of the foregoing remarks, Applicant respectfully submits that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

PATENT
088802-1103 (formerly P41-9321)

Respectfully submitted,

Date: April 2.6, 2001

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Appendix A: Marked up version of the claim amendments, showing the changes made.

Please amend the following claims as indicated by deleting the bracketed material and adding that which is underlined:

17. (Amended) A method according to claim 14 wherein said exogenous gene[s are] is selected from the group consisting of a [wild type] gene[s] naturally contained in the genome of said subject, and [therapeutic] a gene[s] not naturally contained in the genome of said subject.

Appendix B: Pending Claims

14. (Reiterated) A method for modulating the expression of an exogenous gene in a subject containing:

(i) a DNA construct encoding said exogenous gene under the control of a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said subject,

(ii) a receptor which is not normally present in the cells of said subject, wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said steroid or steroid-like hormone response element, and

(iii) ultraspiracle receptor;

said method comprising administering to said subject an effective amount of said associated ligand; wherein said ligand is not normally present in the cells of said subject; and wherein said ligand is not toxic to said subject.

15. (Reiterated) A method according to Claim 14 wherein said receptor not normally present in the cells of the subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

16. (Reiterated) A method according to Claim 15 wherein said receptors are expressed under the control of a tissue specific promoter.

17. (Amended) A method according to claim 14 wherein said exogenous gene is selected from the group consisting of a gene naturally contained in the genome of said subject, and a gene not naturally contained in the genome of said subject.

18. (Reiterated) A method according to Claim 17 wherein said wild type genes are selected from genes which encode gene products:

the substantial absence of which leads to the occurrence of a non-normal state in said subject; or

a substantial excess of which leads to the occurrence of a non-normal state in said subject.

19. (Reiterated) A method according to Claim 17 wherein said therapeutic genes are selected from those which encode gene products:

which are toxic to the cells in which they are expressed; or

which impart a beneficial property to said subject.

35. (Reiterated) A method of inducing the expression of an exogenous gene in a subject containing:

a) a DNA construct encoding an exogenous gene product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject,

b) DNA encoding a receptor which is not normally present in the cells of said subject, under the control of an inducible promoter; wherein said receptor, in the presence of its associated ligand and the ultraspiracle receptor, binds to said hormone response element,

c) ultraspiracle receptor, and

d) the associated ligand for said receptor which is not normally present in the cells of said subject,

said method comprising subjecting a subject to conditions suitable to induce expression of said receptor which is not normally in the cells of said subject.

36. (Reiterated) A method according to claim 35, wherein said ultraspiracle receptor is provided to said subject by a DNA construct encoding said ultraspiracle receptor.

37. (Reiterated) A method according to claim 36, wherein said receptors are expressed under the control of a tissue-specific promoter.

38. (Reiterated) A method according to claim 35, wherein said ultraspiracle receptor is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

39. (Reiterated) A method according to claim 35, wherein said exogenous genes are wild type genes or therapeutic genes.

40. (Reiterated) A method according to claim 39, wherein said wild type genes encode gene products:

(a) the substantial absence of which leads to the occurrence of a non-normal state in said subject, or

(b) a substantial excess of which leads to the occurrence of a non-normal state in said subject.

41. (Reiterated) A method according to claim 39, wherein said therapeutic genes encode gene products:

(a) which are toxic to the cells in which they are expressed, or

(b) which impart a beneficial property to said subject.

42. (Reiterated) A method of inducing expression of an exogenous gene product in a subject containing a DNA construct encoding said product under the control of a hormone response element; wherein said response element is not normally present in the cells of said subject, said method comprising introducing into said subject:

(a) a receptor which is not normally present in the cells of said subject; wherein said receptor, in combination with its associated ligand and ultraspiracle receptor, binds to said hormone response element, activating transcription therefrom,

(b) the ultraspiracle receptor, and

(c) the associated ligand for said receptor.

43. (Reiterated) A method according to claim 42, wherein said receptor not normally present in the cells of said subject and said ultraspiracle receptor are provided to said subject by DNA construct(s) encoding said receptors.

44. (Reiterated) A method according to claim 43, wherein said receptors are expressed under the control of a tissue-specific promoter.

45. (Reiterated) A method according to claim 42, wherein said ultraspiracle receptor is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

46. (Reiterated) A method according to claim 42, wherein said exogenous genes are wild type genes or therapeutic genes.

47. (Reiterated) A method according to claim 46, wherein said wild type genes encode gene products:

(a) the substantial absence of which leads to the occurrence of a non-normal state in said subject, or

(b) a substantial excess of which leads to the occurrence of a non-normal state in said subject.

48. (Reiterated) A method according to claim 46, wherein said therapeutic genes encode gene products:

(a) which are toxic to the cells in which they are expressed, or

(b) which impart a beneficial property to said subject.

49. (Reiterated) A method to distinguish the physiological effect of a first hormone receptor in a host from other hormone receptors in said host which respond to the same ligand, said method comprising:

(a) replacing the ligand binding domain of said first receptor with a ligand binding domain from an exogenous receptor to produce a chimeric receptor maintained under the control of a tissue specific promoter;

wherein said exogenous receptor and the ligand to which the exogenous receptor responds are not normally present in said host; and

wherein said exogenous receptor, in the presence of its associated ligand, binds to a hormone response element, thereby activating said response element, and thereafter

(b) monitoring the production of product(s) whose expression is controlled by said first hormone receptor when said host is exposed to ultraspiracle receptor and ligand to which said exogenous receptor responds.

50. (Reiterated) A method to render mammalian hormone receptor(s) uniquely responsive to a ligand not endogenous to host(s) in which said receptor is normally found, said method comprising:

(a) replacing the ligand binding domain of said receptor with a ligand binding domain from a second receptor;

wherein said second receptor is not normally present in said host; and wherein the ligand to which the second receptor responds is not normally present in said host.

51. (Reiterated) A method according to claim 50, wherein said second receptor is ultraspiracle receptor.

52. (Reiterated) A method according to claim 50, wherein said ultraspiracle receptor has an amino acid sequence that is substantially the same as that set forth in amino acids 1-513 of SEQ ID NO:2.

53. (Reiterated) A method to determine the ligand(s) to which orphan receptor(s) responds, said method comprising:

monitoring a host cell containing a reporter construct and a hybrid receptor for expression of product(s) of said reporter construct upon contacting said cell with potential ligands for said orphan receptor and the ultraspiracle receptor;

wherein said reporter construct comprises a gene encoding

a reporter molecule, operatively linked for transcription to a steroid or steroid-like hormone response element; wherein said response element is not normally present in the cells of said host;

wherein said hybrid receptor comprises:

the N-terminal domain and DNA binding domain of a member of the steroid/thyroid superfamily of receptors, wherein said member is not normally present in the host cells, and wherein said member, in the presence of its associated ligand and ultraspiracle receptor, binds said response element, activating transcription therefrom, and

the ligand binding domain of said orphan receptor.